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EXAMINER

ART UNIT

PAPER NUMBER

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

# Office Action Summary

Application No.

09/680.738

Applicant(s)

EDWARDS ET AL

Examiner

Bronwen Loeb

Art Unit

1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-17 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-17 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4
- 4) ☐ Interview Summary (PTO-413) Paper No(s) \_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other *detailed action*

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### DETAILED ACTION

Claims 1-17 are pending.

#### *Sequence Compliance*

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because sequences were set forth that lack sequence identifiers, no computer readable format (CRF) was filed, no paper sequence was filed and no attorney statement was filed. These sequences include **in Figure 1, specifically "GAL4(1-147)" and "GAL4(768-881)"**. If the Sequence Listing required for the instant application is identical to that of another application, a letter may be submitted requesting transfer of the previously filed sequence information to the instant application. For a sample letter requesting transfer of sequence information, refer to MPEP § 2422.05. Additionally, it is often convenient to identify sequences in figures by amending the Brief Description of the Drawings section (see MPEP § 2422.02).

Applicants are required to comply with all of the requirements of 37 CFR 1.821 through 1.825. Any response to this office action that fails to meet all of these requirements will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F.R. 1.821 through 1.825 did not preclude the continued examination of the application on the merits, the results of which are communicated below.

Alternatively, to preclude having to comply with the sequence rules, it is suggested that Applicant submit a revised Figure 1 wherein "GAL4(1-147)" is replaced with "GAL4bd" and "GAL4(768-881)" is replaced with "GAL4ad". For correction of drawings, see MPEP 608.02(p). Similarly, any reference in the specification to "GAL4(1-147)" or "GAL4(768-881)" should be replaced.

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### ***Drawings***

2. Figure 1 should be designated by a legend such as --Prior Art-- because only that which is old is illustrated. See MPEP § 608.02(g).
3. The drawings are objected to because Figures 4 and 5 present a unit ( $10^{-n}$  M) which is unknown. Also, the dose numbers on the X-axis are decreasing as one goes from left to right. Is the "Dose" supposed to be equal to "n"? In other words, is one of the doses indicated actually  $1 \times 10^{-15}$  M, not  $15 \times 10^{-n}$  M? If so, this should be clarified in the drawing. Correction is required.

### ***Specification***

4. The disclosure is objected to because of the following informalities: on pp. 7 and 8, it seems that the definitions for the abbreviations used in Figures 2 and 3 have been switched. For instance, Figure 2 shows GRE and TRP not ERE and URA3. Figure 3 shows ERE and URA not GRE and TRP1. Related errors appear on p. 17, line 22 and p. 18, lines 1-10. In Table 1 on p. 19, there are no units for the numbers in the table. Are the units supposed to be nanomolar? The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: the specification does not recite or define "Gal4pBD DNA binding domain" or "Gal4pAD transcriptional activation domain", which are used in claim 17.

Appropriate correction is required.

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### ***Claim Objections***

5. Claims 7, 12 and 17 are objected to because of the following informalities: in claim 7, the "with" in line 2 appears to be unnecessary. In claim 11, "mineralocorticoid" is listed twice (lines 2 and 4). In claim 12, "mineralocorticoid" is listed twice (lines 9 and 11). Also in claim 12, "analogue" in the phrase "mineralocorticoid analogue" should be plural. In claim 17, the word "inducible" has been misspelled twice (lines 11 and 20). Also in claim 17, the word "in" in the phrase "the host cell in" in lines 12 and 21 should be replaced with the word "with" to improve the grammar. In claim 17, the abbreviations "Gal4pBD" and "Gal4pAD" should be defined at their first use. In claim 17, lines 7-8 and 15-16, in the phrase "ampicillin or kanamycin resistance genes", "gene" should not be plural. Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for regulation by means of activatable promoters and wherein the first and second interacting molecules are hybrid proteins encoded by chimeric genes, does not reasonably provide enablement for interacting molecules which are anything other than proteins. The specification does not enable any person

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skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are very broad. Claim 1 encompasses a method for detecting an interaction between a first interacting molecule and a second interacting molecule at variable sensitivities, wherein the absolute or relative amounts of the first or second interacting molecule can be regulated by the host cell. The first and second interacting molecule can be anything, including a protein, a DNA, an RNA, a nucleic acid, another macromolecule, a small molecule, a pharmaceutical agent or any other biologically or chemically interacting molecule.

The nature of the invention is a method for detecting an interaction between a first interacting molecule and a second interacting molecule in a host cell, which comprises a detectable reporter gene.

An analysis of the prior art as of the effective filing date of the present application shows a great deal of art dealing with two-hybrid screens wherein the hybrids are proteins. There is, however, scant art dealing with two-hybrid screens wherein the hybrids are not both proteins. There are a few patents directed to identifying molecular

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interactions between protein/DNA, protein/RNA or RNA/RNA interactions (see for instance USP 5,965,368 to Vidal et al). There is scant art dealing with hybrid molecules that comprise another macromolecule, a small molecule, a pharmaceutical agent or any other biologically or chemically interacting molecule wherein two domains, when brought in close proximity to one another, can serve to activate transcription by RNA polymerase.

The relative skill of those in the art of transcription is high.

The area of the invention is unpredictable because there is no a priori expectation that a DNA or an RNA or any other non-protein domain can be found or designed which can activate transcription when in close to proximity to a specific DNA binding domain which is DNA, RNA or any other non-protein molecule.

The present specification provides little or no direction or guidance to support the claimed invention. The specification discloses specific protein DNA binding domains and transcription activation domains but does not teach any specific DNA binding domains and transcription activation, which are DNA, RNA or any molecule other than protein.

The working examples disclosed only encompass regulating the amounts of the first or second hybrid proteins using activatable promoters driving the corresponding chimeric gene.

The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art of the present specification to teach how to make and use the claimed method. In order to determine how to use the

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method for detecting an interaction between two interacting molecules at variable sensitivities, wherein the interacting molecules are anything other than proteins, one would have to create and/or test a huge number of molecules to identify those which can specifically bind to DNA and those which can activate transcription. One would then further have to determine a way to enable the host cell to regulate the absolute or relative amounts of the two non-protein interacting molecules to create the variable sensitivities.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to make and use the claimed methods for detecting an interaction between a first test protein and a second test protein at variable sensitivities wherein the first and second interacting molecules are anything other than proteins.

8. Claims 12-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is based on the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph "Written Description" Requirement published in the Federal Register (Volume 64, Number 244, Pages 71427-71440). Claim 12 is drawn to a method for detecting an interaction between a first test



protein and a second test protein wherein the relative or total amounts of the first or second interacting molecules or macromolecules or small molecules can be regulated by a modulatory agent consisting of at least one of (a) a natural or synthetic, metabolically active or inactive steroid, steroid analogue or steroid mimic....; (b) a membrane-active agent or analogue thereof.....; (c) a small molecular pharmaceutical agent....; and (d) a biomolecular or natural or synthetic biopharmaceutical..... This is a genus claim in terms of small molecules, steroid analogue or steroid mimic and small molecular pharmaceutical agent. The specification mentions, but does not define in detail or provide specific examples of interacting molecules that are small molecules. Based on p. 10, lines 17-21, one may infer this phrase refers to "pharmaceutical agent or any other molecule that contains or may be bound to a molecule containing a DNA binding region or domain". This description however is not specific and detailed regarding the structure of the small molecules suitable for the invention. The specification merely recites "steroid analogue or mimic" on p. 12, lines 3-6 but does not specifically define either term or describe their structure in any detail. The specification mentions on p. 15, line 23-p. 16, line 4, small molecular pharmaceutical agent and provides a generic list of such agents, which are characterized by function ("antimicrobial agent", "co-repressor", etc.). No specific agent examples are provided for any of these generic categories, nor is any structural information disclosed. This disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims as one of skill in the art cannot envision all the small molecules, steroid analogues or steroid mimics, or small molecular

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pharmaceutical agents based on the teachings in the specification. Therefore, the specification does not describe the claimed small molecules, steroid analogues or steroid mimics, or small molecular pharmaceutical agents in such full, clear, concise and exact terms so as to indicate that Applicant has possession of these molecules at the time of filing the present application. Thus, the written description requirement has not been satisfied.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite for several reasons. First, the preamble recites a first test protein and a second test protein however the body of the claim recites a first interacting molecule and a second interacting molecule and a first or second macromolecule but never recites first test protein or second test protein. Second, the claim lacks a step which clearly relates back to the preamble; the method steps lead one to determining the extent to which the detectable reporter gene has been activated but does not mention detecting an interaction between a first and second test protein. Third, the phrases "comprising a region capable of binding DNA" (lines 6-7), "a region capable of transcriptional activation" (line 8) and "the capacity to regulate" (line 9) are vague and indefinite as "capable of" denotes a latent ability which may or may not be

observed in the invention. Fourth, it is unclear how the host cell will be able to regulate the relative amounts if it can only regulate the amount of one or the other of the first and second macromolecules; the claim as written recites "regulate the absolute or relative amounts of the first *or* second macromolecules" (lines 9-10) and "regulating the amounts of the first *or* the second macromolecule" (line 11) {emphasis added}.

Claim 1 recites the limitation "the first or second macromolecules or small molecules" in lines 10-11. There is insufficient antecedent basis for this limitation in the claim.

Claim 3 is vague and indefinite because it recites "another molecule, a small molecule, a pharmaceutical agent or another biologically or chemically interacting molecule" which phrases are very extremely broad and are not clearly defined in the specification. Therefore one cannot determine the metes and bounds of the claim.

Claims 4 and 7 are vague and indefinite for reciting "capable of being transcribed". The phrase "capable of" denotes a latent ability that may or may not be observed in the invention.

Claim 7 is vague and indefinite because it recites "the first interacting molecule is provided by introducing into the host cell with a second chimeric gene". Does this recitation mean that the second chimeric gene encodes the first interacting molecule? Furthermore, is "a second chimeric gene" different from the second chimeric gene recited in claim 4?

Claim 9 recites the limitation "the second exogenously activated promoter" in line 1. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to amend the phrase to recite "the second exogenously activatable promoter".

Claim 11 is vague and indefinite for using improper Markush language. A Markush group should end with "and" (not "or") and there should be only a single "and" in the group.

Claims 11 and 12 are vague and indefinite for reciting "retinoids" as a steroid. Retinoids are not steroids; they are vitamin A metabolites.

Claims 11 and 12 are vague and indefinite for reciting "other agents capable of interacting with steroid responsive elements" as a possible steroid. Steroid receptors, not the steroids themselves, interact with steroid responsive elements.

Claims 11 and 12 are vague and indefinite for reciting "steroid complementary to orphan receptors". Steroids bind to receptors; they are not complementary to them.

Claim 12 is vague and indefinite as the phrase "continuous or discontinuous adjustment of a selected reporter sensitivity" is not a term of art nor is it defined in the specification.

Claim 12 is also vague and indefinite as it employs improper Markush group language. This rejection would be overcome by amending the claim to recite "and" at the end of group (c), p. 36, line 2.

Claim 13 is vague and indefinite as the phrases "continuously adjustable" and "plurally stepped dose-responsive basis" are not terms of art nor are they defined in the specification.

Claim 14 is vague and indefinite as the phrase "discontinuously adjustable" is not a term of art nor is it defined in the specification.

Claim 15 is vague and indefinite as the phrase "sensitivity is adjustable both discontinuously and continuously" is not a term of art nor is it defined in the specification.

Claim 16 is vague and indefinite in reciting "an agent capable of interfering". The phrase "capable of" denotes a latent ability that may or may not be observed in the invention.

Claim 17 is vague and indefinite for reciting "containing" as its transitional phrase. "Containing" is not legally defined as an open or closed term. It is suggested that the claim be amended to recite "comprising" or "consisting of" as appropriate. In line 1, "the first" should be amended to recite "the first integrated reporter" to clarify what "the first" refers to. The meaning of the phrase "being suitable when activated, for the rescue of nutrient auxotrophies" is unclear. The phrase "capable of activating" recited in lines 13 and 22 is vague and indefinite as it denotes a latent ability which may or may not be observed in the invention. The phrase "activating inducing" on line 13 is vague and indefinite as the meaning of this phrase is unclear.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as

to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 12 recites the broad recitation "(a) a natural or synthetic, metabolically active or inactive steroid, steroid analogue or steroid mimic", and the claim also recites "including glucocorticoids, dexamethasone, cortisone, cortisol..." which is the narrower statement of the range/limitation. Claim 12 has three additional instances of a broad recitation followed by a narrower statement in groups (b), (c), and (d).

### ***Claim Rejections - 35 USC § 102***

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Finley et al ("Two-hybrid analysis of genetic regulatory networks" in *The Yeast Two-Hybrid System*, Bartel et al eds. 1997 Oxford University Press pp. 197-214). Finley et al teach two-hybrid assays for use in protein-protein interactions studies wherein a host cell

comprises a reporter gene (LEU2 and lacZ) in response to the interaction of two hybrid proteins; both hybrid proteins are encoded by chimeric genes and both may be expressed from an inducible promoter (GAL1 promoter) which enables one to regulate the amount of protein present in the cell. The sensitivity is variable as one can have an uninduced, basal level of hybrid protein expression or an induced level of expression by exogenous addition of the inducer, galactose. See entire document, especially pp. 199-200 "Interaction Mating".

***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Finley et al as applied to claims 1-9 above, and in view of Schena et al (Methods in Enzymology (1991) 194:389-398). Finley et al does not teach a method wherein the exogenous activator is a steroid, or wherein the reporter sensitivity is one of a continuous or discontinuous adjustment. Schena et al teach an inducible promoter system for based on steroid receptors, steroid response elements and the cognate steroid for use in expressing genes in yeast, which provides intermediate levels of induction possible by titrating the levels of hormone in the culture medium. At the time the invention was made, it would have been obvious to one of ordinary skill in the art to use the steroid inducible promoter system of Schena et al in the method taught by Finley et al. One of ordinary skill in the art would have been motivated to do so in order to obtain the advantages of a steroid inducible promoter system as taught by Schena et al; steroid hormones are gratuitous inducers in yeast and therefore have little or no effect on the expression of endogenous genes and also offer rapid induction kinetics. See Introduction and pp. 394-397, especially 396-397. In addition, Finley et al teach that use of an inducible promoter such as GAL1 is useful to express toxic proteins and also helps eliminate false positives. See p.199, Interaction mating.

### ***Conclusion***

Claims 1-15 are rejected. Claims 16 and 17 are free of prior art.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for



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the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from 10:00 AM to 6:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to Dianiece Jacobs, Patent Analyst whose telephone number is (703) 305-3388.

Bronwen M. Loeb, Ph.D.  
Patent Examiner  
Art Unit 1636

July 26, 2001

  
ROBERT A. SCHWARTZMAN  
PRIMARY EXAMINER